13 Receptor Down-Regulation in
the Failing Human Heart

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Unlike other critical organs, the heart can dramatically increase its functional capacity almost instantly. The adrenergic nervous system is responsible for this impressive modulation of activity, effectively controlling the contractile state of the heart on a beat-to-beat basis.

In the late 1970s, I became interested in the cardiotoxic effects of cardiac norepinephrine (NE) and histamine release. My colleagues Robert Ginsburg and Wayne Minobe and I decided to examine in detail the 13 adrenergic receptor pathway(s) in the failing heart, testing the hypothesis that in the failing heart, testing the hypothesis that the failing heart experiences a high level of cardiac adrenergic drive, which then results in receptor pathway desensitization. We subsequently demonstrated that although both (3, and R2 receptors are present in the human heart, the receptor which down-regulates is the 3, receptor. Although we and others also demonstrated numerous additional abnormalities of this pathway, the most consistent abnormality present across all forms of dilated cardiomyopathy is down-regulation of B1 receptors. Finally, the explanation for this form of agonist-induced receptor down-regulation appears to be altered gene expression leading to a decrease in 13, receptor mRNA abundance.

Evidence that the failing human heart is exposed to and senses a high level of adrenergic activity provided part of the pathophysiologic rationale for the treatment of human heart failure with antiadrenergic agents. It also led to the development of short-term strategies designed to restore 13 adrenergic pathway function in situations where higher levels of inotropic action are desirable. I believe this paper is frequently cited because it was the first reproducible work that demonstrated a molecular or nonstructural abnormality in a contractility-regulating mechanism in the failing human heart. It was also the first study to extensively use human ventricular myocardium as an experimental model, and it probably demonstrated to many investigators the feasibility and utility of the "human approach" to the problem of heart failure.